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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/706,690 | 11/07/2000 | Hyun Chul Lee | 0452-0110P | 8465 |

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| EXAMINER |
|---|
| BUNNER, BRIDGET E |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1647 | 12 |

DATE MAILED: 02/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/706,690 | Applicant(s) LEE ET AL. | |
|---|---|---|---|
| | Examiner Bridget E. Bunner | Art Unit 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *3-7 and 18-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 8-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-25* are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Bridget E. Bunner, Group Art Unit 1647.

### *Status of Application, Amendments and/or Claims*

The amendment of 01 May (Paper No. 3) has been entered in full.

### *Election/Restrictions*

Applicant's election with traverse of Group I, claims 1-17, drawn to single chain insulin analog compound, nucleic acids encoding said compound, vectors, and host cells in Paper No. 10 (26 December 2001) is acknowledged. The traversal is on the ground(s) that a serious burden has not been placed on the examiner to consider all the claims in a single application. Applicant contends that a review of the subject matter set forth in claims 1-25 would include a review of both class 435 and class 514 and that a different field of search does not exist with regard to the claims of the present invention. Applicant also asserts that because of the close inter-relationship between the various species of the present application, it is believed that all of the species are properly examinable in a single application. This is not found persuasive. As discussed in the previous Office Action (Paper No. 8, 26 November 2001), Inventions I and II-III are related as product and process. The methods of Groups II-III could be practiced with another materially different product, such as human insulin, rather than with the insulin analog or vectors of Group I. Additionally, the product of Group I could used in materially different methods other than the methods of Inventions II-III, such as in the production of antibodies. Each invention is unique, requiring a unique search of the prior art. Searching the product and both methods in this single patent application would provide an undue search burden on the examiner and the USPTO's

resources because of the non-coextensive nature of these searches. Furthermore, the inventions of Groups II and III require a divergent literature search, with no reason to believe that the searches would be co-extensive. Groups II and III are different methods requiring different method steps, wherein each is not required, one for another. For example, Invention II requires search and consideration of efficacy of therapy of administration of DNA encoding a single-chain insulin analog to a patient suffering from diabetes, which is not required by the other invention. Invention III requires search and consideration of efficacy of therapy of administration of a single-chain insulin analog to a patient suffering from diabetes, which is not required by the other inventions. Furthermore, each of the species of joining peptides ("X") in the claims requires a unique search of the prior art. Searching all of the species in a single patent application would provide an undue search burden on the examiner and the USPTO's resources because of the non-coextensive nature of these searches.

The requirement is still deemed proper and is therefore made FINAL.

Claims 3-7 and 18-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected group and species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10 (26 December 2001).

Claims 1-2 and 8-17 are under consideration in the instant application. The claims read upon the elected species of "X": gly-gly-gly-pro-gly-lys-arg.

***Priority***

1. Receipt is acknowledged of papers filed under 35 U.S.C. 119 (a)-(d) based on an application filed in Korea on 02 October 2000. Applicant has not complied with the

requirements of 37 CFR 1.63(c), since the oath, declaration or application data sheet does not acknowledge the filing of any foreign application. A new oath, declaration or application data sheet is required in the body of which the present application should be identified by application number and filing date. Please also note that a claim for priority under 35 U.S.C. 119(a)-(d) cannot be based on said application, since the United States application was filed more than twelve months after the foreign application.

***Drawings***

2. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

***Specification***

3. The disclosure is objected to because of the following informalities:

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "A SINGLE-CHAIN INSULIN ANALOG AND A POLYNUCLEOTIDE SEQUENCE ENCODING THE ANALOG".

5. The specification refers to Table 1 at pg 20, lines 13-25. However, Table 1 is not present in the application. (Please note that this issue could be overcome by removing the references to Table 1.)

Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-2 and 8-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a single-chain insulin analog compound of formula (I) having the properties of greater insulin receptor binding activity than proinsulin and less insulin receptor binding activity than insulin: B chain- X- A chain (I) wherein: B and A chains are the human insulin chains and X is a joining peptide of from 5 to 18 amino acids and has a sequence of Gly-Gly-Gly-Pro-Gly-Lys-Arg (SEQ ID NO: 1), does not reasonably provide enablement for a single-chain insulin analog compound of formula (I) having the properties of greater insulin binding activity than proinsulin and less insulin receptor binding activity than insulin: B chain- X- A chain (I) wherein: B and A chains are the human insulin chains, respectively, or functional analogs thereof; and X is a joining peptide of from 5 to 18 amino acids. Additionally, the specification, while being enabling for polynucleotide comprising the nucleic acid sequence of SEQ ID NO: 3 that encodes the single-chain insulin analog, does not provide enablement for a polynucleotide encoding the single-chain insulin analog. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Specifically, claims 1-2 and 8-17 are directed to a single-chain insulin analog compound having the properties of greater insulin receptor binding activity than proinsulin and less insulin receptor binding activity than insulin : B chain-X-A chain and wherein B and A chains are the human insulin chains and X is a joining peptide from 5 to 18 amino acids. The claims are also directed to polynucleotide encoding the single-chain insulin analog, a recombinant vector, and a cell line transfected with the vector.

The specification teaches that single-chain insulin analog 1 (SIA-1) DNA encoding the Gly-Gly-Gly-Pro-Gly-Lys-Arg sequence of SEQ ID NO: 1 in the linker region of SIA is generated by PCR (pg 13, lines 20-23). The gene encoding SIA-I (SEQ ID NO: 3) is inserted into the pET plasmid and used to transform *E. coli* BL21 (DE3) cells. SIA-I is expressed and purified (pg 14, lines 1-19). The specification discloses that 8-10 week-old male Sprague-Dawley rats are fasted and SIA protein or the same volume of saline as a control are injected subcutaneously. Blood is obtained from the tail vein of each rat and the glucose level determined and 30 min, 1, 2, 3, and 4 h after administration of SIA (pg 15, lines 1-22). The specification teaches that the receptor binding activity of SIA-I is 12-fold higher than that of proinsulin and 3- to 4-fold lower than that of insulin. Also, the glucose uptake activity of SIA-I is 16-fold higher than that of proinsulin and 4- to 5-fold lower than that of insulin (pg 20, lines 13-25). Although the specification teaches the generation of other single-chain analogs at pg 14, lines 20-30, there is no guidance as to the number of repeating "X" linkers joined together to make each analog. The specification also does not disclose any functional characteristics of any SIA analogs, other than that of the claimed SIA-I analog. There is no guidance in the specification of any polynucleotide sequence encoding a SIA analog other than the nucleic acid sequence of SEQ ID NO: 3, encoding SIA-I. Furthermore, the specification does not disclose any functional analogs of the human A and B human insulin chains.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can

be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations of the insulin A and B chain analogs, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

***Conclusion***

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Shin et al. GB 2298206A

Chance et al. EP 0741188 A2

Shin et al. (U.S. Patent 5,962,267)

* Lee et al. Nature 408 : 483-488, 2000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BEB
Art Unit 1647
February 19, 2002

Elizabeth C. Kemmerer

ELIZABETH C. KEMMERER
PRIMARY EXAMINER